Measles Vaccination Coverage and Cases among Vaccinated Persons

Christian L. Althaus, Marcel Salathé

Author affiliations: University of Bern, Bern, Switzerland (C.L. Althaus); Pennsylvania State University, University Park, Pennsylvania, USA (M. Salathé)

DOI: http://dx.doi.org/10.3201/eid2108.150284

To the Editor: In December 2014, a measles outbreak that had started at Disneyland Park in Anaheim, California, USA, and subsequently spread to numerous states garnered substantial media attention in the United States. In 2014, the US Centers for Disease Control and Prevention reported the highest number of measles cases (644) since the disease had been declared eliminated from the United States in 2000 (*1*). This number is still relatively lower than the numbers reported from 30 countries of the European Union and the European Economic Area; the highest numbers of measles cases in 2013 were from the Netherlands (2,499 cases), Italy (2,216), the United Kingdom (1,900), and Germany (1,772) (*2*). There is widespread concern that increasing hesitancy to vaccinate in the United States might lead to outbreaks as large as the ones in Europe.

Measles vaccine is highly effective, and analyses of a large measles outbreak at a school in Germany have shown that receipt of ≥1 doses of vaccine can prevent infection in up to 99% of persons (*3*,*4*). One might therefore be tempted to think that the proportion of measles case-patients who had been vaccinated must be very small. However, when vaccination rates are high, most persons exposed to an infected person will have received ≥1 doses of vaccine. As a consequence, the expected proportion of persons who had received ≥1 doses of vaccine among reported measles case-patients will be substantially higher than 1%.

One can derive a simple quantitative relationship between vaccination coverage and the proportion of case-patients who had been vaccinated. Assuming vaccination coverage of v and vaccine effectiveness of α, the proportion of the population who are susceptible to measles infection is $1 - \alpha v$. If all susceptible persons are at the same risk of getting infected, the proportion of vaccinated persons among all case-patients will be $v(1 - \alpha)/(1 - \alpha v)$. This equation is similar to the screening method that has been used to calculate vaccine effectiveness on the basis of the proportion of case-patients who were vaccinated and vaccination coverage (*5*). Perhaps somewhat counterintuitive at first, the proportion of vaccinated measles case-patients increases with vaccination coverage (Figure).

We hypothesized that the observed proportion of measles case-patients who had been vaccinated can be used to infer the vaccination coverage in a population at risk (Figure). To this end, we assume a vaccine effectiveness of 99% among persons who had received ≥1 doses (*3*,*4*). In 2013, countries in the European Union/European Economic Area reported 9,708 measles case-patients for whom vaccination status was known (*2*). Of those, 11.8% had received ≥1 doses of measles vaccine. On the basis of the relationship derived above, this proportion corresponds to an expected vaccination coverage of 93.1% who had received ≥1 doses, which is consistent with reported numbers. Switzerland reported 3,850 measles case-patients with known vaccination status from August 2006 through June 2009; of these, 7.0% had been vaccinated with ≥1 doses (*8*). The inferred vaccination coverage of 88.3% is very close to the reported national level of 87.0% for receipt of ≥1 doses at 2 years of age (*8*). In contrast, the most recent numbers from the United States suggest that vaccination coverage for receipt of ≥1 doses is still well over 90%.

Various complexities might affect the relationship between vaccination coverage in a community and the proportion of case-patients who had been vaccinated. First, we assume a vaccine effectiveness of 99% among persons who received ≥1 doses. Other estimates indicate that

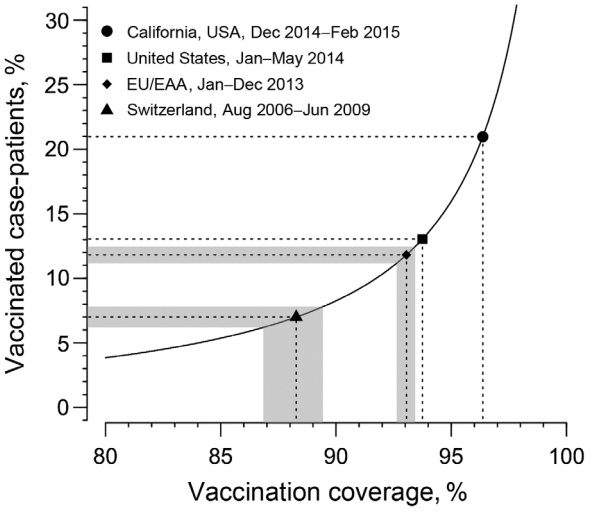

Figure. Relationship between vaccination coverage with ≥1 doses and the proportion of measles case-patients who had been vaccinated. The observed numbers of vaccinated case-patients can be used to infer the vaccination coverage for different populations. Of 62 (21.0%) measles case-patients with known vaccination status in California, USA, 13 had received ≥1 doses (*6*). Of 230 (13.0%) case-patients with known vaccination status in the United States during January–May 2014, a total of 30 had received ≥1 doses (*7*). Vaccine effectiveness is assumed to be 99% (*3*,*4*). The shaded areas for the countries of the European Union (EU) and European Economic Area (EEA), and Switzerland correspond to the 95% CIs. 95% CIs are omitted for California and the United States because of the small sample sizes.

vaccine effectiveness is 92% for persons who received 1 dose and 95% for those who received 2 doses (*9*). Assuming that vaccine effectiveness is lower shifts the curve (Figure) to the left and would result in a lower estimate of vaccination coverage. Second, different numbers of persons who received 1 and 2 doses complicate the identification of overall vaccine effectiveness. Third, vaccination status is unknown for some measles case-patients. The proportion of nonvaccinated persons among those case-patients might be higher than that among those known to be vaccinated, also leading to a lower estimate of vaccination coverage. Finally, nonvaccinated persons might be clustered together, and their risk for infection could be higher than that for the general population (*10*). This scenario would imply that the estimated vaccination coverage does not reflect the general population but instead corresponds to a clustered subpopulation among whom vaccination rates are lower. The effects of these complexities warrant further investigation. However, as the examples demonstrate, a model ignoring those effects is in good agreement with empirical data.

Our analysis suggests that the number of vaccinated measles case-patients should be closely followed through surveillance programs. A continuous decrease in the proportion of measles case-patients who had been vaccinated over the years could indicate a decrease in vaccination rates. Conversely, an increase in the proportion of measles case-patients who had been vaccinated would demonstrate the effectiveness of ongoing efforts to increase vaccination rates and could serve as a benchmark toward measles elimination.

C.L.A. received funding through an Ambizione grant from the Swiss National Science Foundation (grant 136737).

References

1. Centers for Disease Control and Prevention. Measles cases and outbreaks [cited 2015 Feb 13]. http://www.cdc.gov/measles/cases-outbreaks.html
2. European Centre for Disease Prevention and Control. Surveillance report, measles and rubella monitoring, February 2014 [cited 2015 Apr 8]. http://ecdc.europa.eu/en/publications/Publications/measles-rubella-monitoring-february-2014.pdf
3. Wichmann O, Hellenbrand W, Sagebiel D, Santibanez S, Ahlemeyer G, Vogt G, et al. Large measles outbreak at a German public school, 2006. Pediatr Infect Dis J. 2007;26:782–6. http://dx.doi.org/10.1097/INF.0b013e318060aca1
4. van Boven M, Kretzschmar M, Wallinga J, O'Neill PD, Wichmann O, Hahné S. Estimation of measles vaccine efficacy and critical vaccination coverage in a highly vaccinated population. J R Soc Interface. 2010;7:1537–44. http://dx.doi.org/10.1098/rsif.2010.0086
5. Orenstein WA, Bernier RH, Dondero TJ, Hinman AR, Marks JS, Bart KJ, et al. Field evaluation of vaccine efficacy. Bull World Health Organ. 1985;63:1055–68.
6. Centers for Disease Control and Prevention. Measles—California, December 2014–February 2015. MMWR Morb Mortal Wkly Rep. 2015;64:153–4.
7. Centers for Disease Control and Prevention. Measles—United States, January 1–May 23, 2014. MMWR Morb Mortal Wkly Rep. 2014;63:496–9.
8. Richard JL, Masserey Spicher V. Large measles epidemic in Switzerland from 2006 to 2009: consequences for the elimination of measles in Europe. Euro Surveill. 2009;14:19443.
9. Marin M, Nguyen HQ, Langidrik JR, Edwards R, Briand K, Papania MJ, et al. Measles transmission and vaccine effectiveness during a large outbreak on a densely populated island: implications for vaccination policy. Clin Infect Dis. 2006;42:315–9. http://dx.doi.org/10.1086/498902
10. Salathé M, Bonhoeffer S. The effect of opinion clustering on disease outbreaks. J R Soc Interface. 2008;5:1505–8. http://dx.doi.org/10.1098/rsif.2008.0271

Address for correspondence: Christian L. Althaus, Institute of Social and Preventive Medicine, University of Bern, Finkenhubelweg 11, 3012 Bern, Switzerland; email: christian.althaus@alumni.ethz.ch

Lassa Virus in Multimammate Rats, Côte d'Ivoire, 2013

Leonce Kouadio, Kathrin Nowak, Chantal Akoua-Koffi, Sabrina Weiss, Bernard K. Allali, Peter T. Witkowski, Detlev H. Krüger, Emmanuel Couacy-Hymann, Sébastien Calvignac-Spencer, Fabian H. Leendertz

Author affiliations: Robert Koch Institut, Berlin, Germany (L. Kouadio, K. Nowak, S. Weiss, S. Calvignac-Spencer, F.H. Leendertz); Laboratoire Central de la Pathologie Animal, Bingerville, Côte d'Ivoire (L. Kouadio, E. Couacy-Hymann); Université Alassane Ouattara de Bouake, Bouake, Côte d'Ivoire (C. Akoua-Koffi); European Centre for Disease Prevention and Control, Stockholm, Sweden (S. Weiss); Public Health England, London, UK (S. Weiss); Institut Pasteur de Côte d'Ivoire (B.K. Allali); Charité School of Medicine, Berlin (P.T. Witkowski, D.H. Krüger)

DOI: http://dx.doi.org/10.3201/eid2108.150312

To the Editor: Lassa fever is a zoonosis caused by Lassa virus (LASV; family Arenaviridae, genus Lassavirus). The primary reservoir of LASV is the multimammate rat (Mastomys natalensis), which is found throughout sub-Saharan Africa. LASV outbreaks among humans occur only in West Africa in 2 noncontiguous areas: 1 in Guinea, Liberia, and Sierra Leone; and 1 in Nigeria. Rare cases and evidence of exposure of humans have been documented in neighboring countries (i.e., Benin, Burkina Faso, Côte d'Ivoire, Ghana, Mali, and Togo) (*1*). LASV RNA has been detected in only 4 patients: 1 in Germany who had traveled in Burkina Faso, Côte d'Ivoire, and Ghana (*2*); 1 in the United Kingdom who had returned from Mali (*3*); and 2 in

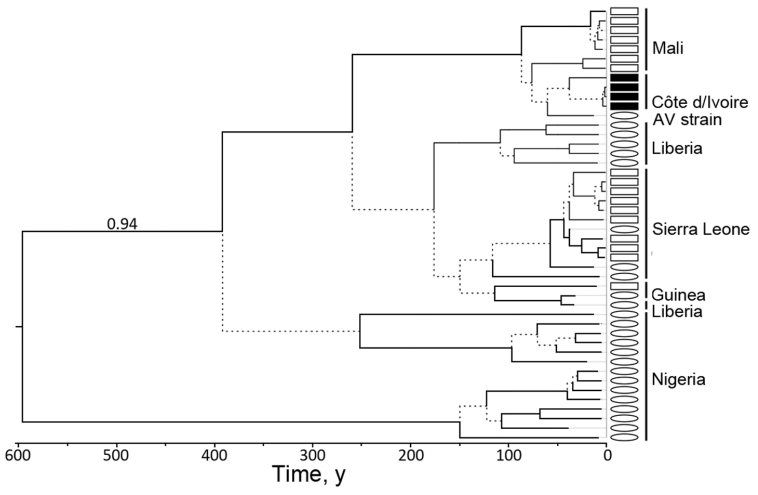

Figure. Bayesian chronogram of Lassa virus (LASV) sequences determined on the basis of a fragment of the large genomic segment. Branches receiving posterior probability values <0.95 and bootstrap values <50 (poorly supported) are dashed. LASV sequences of human origin are indicated by ovals, and those of multimammate rats are indicated by squares. Sequences reported in this study are indicated by black squares. This tree was built under the assumption of a molecular clock and is therefore rooted. The numerical value on the tree's most basal branch is the root posterior probability of this branch; it supports the notion that LASV sequences from Nigeria and other countries are not reciprocally monophyletic. GenBank accession nos. of sequences used for phylogenetic analyses are shown in online Technical Appendix Table 2 (http://wwwnc.cdc.gov/EID/article/21/8/15-0312-Techapp.pdf). AV strain indicates the strain from a German patient.

Ghana, for whom no viral sequence was available because detection was performed by reverse transcription PCR only (*4*). In the region in Mali where the patient from the United Kingdom was infected, identical LASV sequences were found in multimammate rats (*5*). The sequence of the strain identified from the patient in Germany, who was designated AV, is the closest known relative of the clade formed by sequences from Mali (*5*). However, LASV was not found in its natural host in any of the countries visited by patient AV (*6,7*).

For a study investigating zoonotic pathogens in rural habitats, we caught small mammals in 3 ecologic zones of Côte d'Ivoire: 1) dry bushland in northern Côte d'Ivoire, around Korhogo (*2*); semiarid bushland in central Côte d'Ivoire, around Bouake; and rainforest in southwestern Côte d'Ivoire, near the Taï National Park (*3*) (online Technical Appendix Figure, http://wwwnc.cdc.gov/EID/article/21/8/15-0312-Techapp.pdf). Traps were installed within and around 15 villages and enabled the capture of 27 eulipotyphlans and 254 rodents during August–October 2013. Animals were assigned at the genus level in the field on the basis of morphology. For 88% of them, assignment could later be refined to the species level by sequencing a fragment of the mitochondrial cytochrome *b* gene. A total of 14 animal species representing 8 genera were detected. All host sequences were deposited in Dryad (http://www.datadryad.org/; online Technical Appendix Table 1). Multimammate rats were the dominant commensals at all sampling locations, comprising 64.5% of the overall sample (online Technical Appendix Figure).

Tissue samples were collected from all animals according to standard protocols. Total nucleic acids were extracted from lung samples and tested for the presence of LASV RNA by using a real-time PCR system amplifying a 400-bp fragment of the large genomic segment (*8*) (online Technical Appendix). LASV RNA was detected in 4 of 18 specimens of *M. natalensis* captured in Gbalôhô, near Korhogo (online Technical Appendix Figure). This site is much farther north in Côte d'Ivoire than previously examined sites (*6*). The 4 PCR-positive animals were 3 males and 1 female that were all captured indoors, 3 in the same house. PCR products were sequenced according to the Sanger method (GenBank accession nos. LN823982–LN823985). According to phylogenetic analyses performed in maximum likelihood and Bayesian frameworks (online Technical Appendix), LASV sequences identified in multimammate rats from Côte d'Ivoire formed a robust clade with sequences from the human AV strain and the LASV infecting multimammate rats in southern Mali (bootstrap 97, posterior probability 1.00; Figure). This phylogenetic placement opens up the possibility that patient AV was infected during her travel through Côte d'Ivoire, possibly in or near the city of Korhogo. Tip date calibration of Bayesian analyses showed that the most recent common ancestor of all LASV sequences from Côte d'Ivoire and Mali circulated ≈90 years ago (Figure; online Technical Appendix Table 2).

Further studies will be needed to investigate the geographic distribution of LASV in Côte d'Ivoire and the frequency of human infections. The current lack of diagnosed cases in the area may be caused by underreporting. Sensitization campaigns are needed to increase awareness of the risk for LASV infection among the local population and to improve detection of cases by health workers.

Acknowledgments

We thank the Ministry of Health of Côte d'Ivoire and the directors of the Laboratoire National d'Appui au Développement Agricole and Centre Hospitalier Universitaire, Bouake, Côte d'Ivoire for their support and permission to conduct the study. We also thank the chiefs of the various villages where captures were performed

for their permission and support; the Swiss Research Center, Côte d'Ivoire, for logistical support; A. Krou, Y. Djambra, B. Gragnon, F. Beudjé, and M. Coulibaly for technical support during field missions; and U. Thiesen, K. Merkel, A. Sachse, and the sequencing laboratory team of the Robert Koch Institute for laboratory support.

This work was funded by the Deutsche Forschungsgesellschaft grant LE1813/7-1.

References

1. Sogoba N, Feldmann H, Safronetz D. Lassa fever in West Africa: evidence for an expanded region of endemicity. Zoonoses Public Health. 2012;59(Suppl 2):43–7. http://dx.doi.org/10.1111/j.1863-2378.2012.01469.x
2. Günther S, Emmerich P, Laue T, Kuhle O, Asper M, Jung A, et al. Imported lassa fever in Germany: molecular characterization of a new lassa virus strain. Emerg Infect Dis. 2000;6:466–76. http://dx.doi.org/10.3201/eid0605.000504
3. Atkin S, Anaraki S, Gothard P, Walsh A, Brown D, Gopal R, et al. The first case of Lassa fever imported from Mali to the United Kingdom, February 2009. Euro Surveill. 2009;14: pii:19145.
4. Dzotsi EK, Ohene SA, Asiedu-Bekoe F, Amankwa J, Sarkodie B, Adjabeng M, et al. The first cases of Lassa fever in Ghana. Ghana Med J. 2012;46:166–70.
5. Safronetz D, Lopez JE, Sogoba N, Traore SF, Raffel SJ, Fischer ER, et al. Detection of Lassa virus, Mali. Emerg Infect Dis. 2010;16:1123–6.
6. Coulibaly-N'Golo D, Allali B, Kouassi SK, Fichet-Calvet E, Becker-Ziaja B, Rieger T, et al. Novel arenavirus sequences in *Hylomyscus* sp. and *Mus* (*Nannomys*) *setulosus* from Côte d'Ivoire: implications for evolution of arenaviruses in Africa. PLoS ONE. 2011;6:e20893. http://dx.doi.org/10.1371/journal.pone.0020893
7. Kronmann KC, Nimo-Paintsil S, Guirguis F, Kronmann LC, Bonney K, Obiri-Danso K, et al. Two novel arenaviruses detected in pygmy mice, Ghana. Emerg Infect Dis. 2013;19:1832–5. http://dx.doi.org/10.3201/eid1911.121491
8. Lecompte E, Fichet-Calvet E, Daffis S, Koulemou K, Sylla O, Kourouma F, et al. *Mastomys natalensis* and Lassa fever, West Africa. Emerg Infect Dis. 2006;12:1971–4. http://dx.doi.org/10.3201/eid1212.060812

Address for correspondence: Fabian H. Leendertz, Robert Koch Institut, Seestrasse 10, 13353 Berlin, Germany; email: leendertzf@rki.de

Rickettsia felis Infection among Humans, Bangladesh, 2012–2013

Faria Ferdouse, Muhammad Akram Hossain, Shyamal Kumar Paul, Salma Ahmed, Md Chand Mahmud, Rajib Ahmed, A.K.M. Fazlul Haque, M. Nur-a-Alam Khan, Souvik Ghosh, Noriko Urushibara, Nobumichi Kobayashi

Author affiliations: Mymensingh Medical College, Mymensingh, Bangladesh (F. Ferdouse, M.A. Hossain, S.K. Paul, S. Ahmed, M.C. Mahmud, R. Ahmed, A.K.M.F. Haque, M.N.A. Khan); Sapporo Medical University School of Medicine, Sapporo, Japan (S. Ghosh, N. Urushibara, N. Kobayashi); Ross University School of Veterinary Medicine, St. Kitts, West Indies (S. Ghosh)

DOI: http://dx.doi.org/10.3201/eid2108.150328

To the Editor: *Rickettsia felis*, which belongs to the spotted fever group of rickettsiae, causes febrile illness in humans. The main vector of this bacterium is the cat flea (*Ctenocephalides felis*). Since publication of reports of *R. felis* as a putative pathogen of humans in the United States in 1994, *R. felis* infection in humans worldwide has been increasingly described, especially in the Americas, Europe, Africa, and eastern Asia (*1*,*2*). *R. felis* infection is common among febrile patients (≈15%) in tropical Africa (*3*) and among apparently healthy persons in eastern coastal provinces of China (*4*). However, little is known about prevalence of *R. felis* infection of humans in southern Asia, although 3 serologically diagnosed cases in Sri Lanka have been described (*5*) and *R. felis* has been detected in rodent fleas in Afghanistan (*6*). Hence, we conducted a cross-sectional study in Bangladesh to explore the presence of rickettsial pathogens among patients with fever of unknown origin.

Study participants were 150 patients at Mymensingh Medical College (MMC) hospital in Mymensingh, north-central Bangladesh, from July 2012 through January 2014, and 30 healthy control participants from the staff at the same college. Selected patients met the following criteria: 1) fever (axillary temperature >37.5°C) for >15 days that did not respond to common antimicrobial drug therapy; 2) any additional clinical features including headache, rash, lymphadenopathy, myalgia, and eschars on skin; and 3) titer according to the Weil-Felix test (antibodies against any of 3 *Proteus* antigens) of >1:80. Patients with evident cause of fever (e.g., malaria diagnosed by blood smear or immunochromatography) were excluded from the study. This research was approved by the college institutional review board, and informed consent was obtained from patients (or guardians) and healthy controls before their entry into the study.

Venous blood samples were aseptically collected from the patients, and DNA was extracted by conventional method by using proteinase K and sodium dodecyl sulfate. Nested PCR selective for the 17-kDa antigen gene was used to screen for rickettsiae according to the method described previously (*7*); ≈100 ng of DNA in a 50-mL reaction mixture was used. For each PCR, a negative control (water) was included and utmost care was taken to avoid contamination. Among the 150 samples tested, results were positive with a 232-bp amplified product for 69 (46%) and negative for all controls.

PCR products from 20 samples were randomly selected for sequence analysis. All nucleotide sequences from

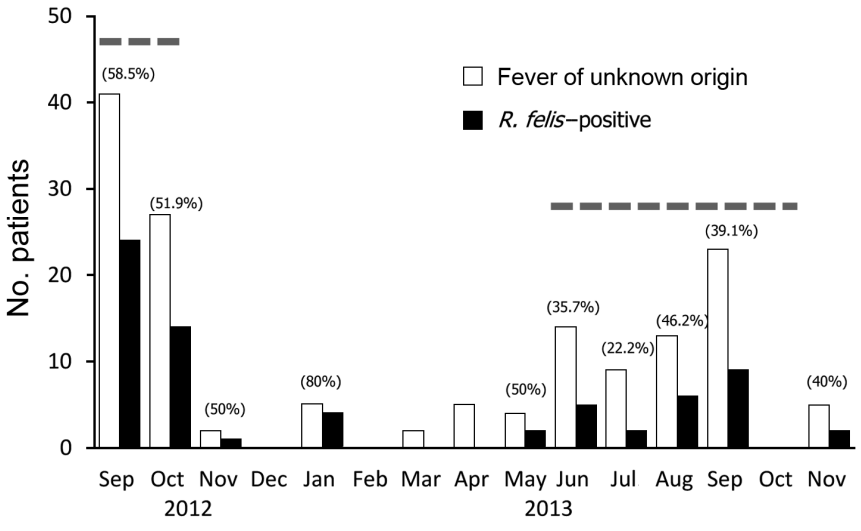

Figure. Number of patients with fever of unknown origin and *Rickettsia* felis–positive cases in the Mymensingh Medical College hospital, Bangladesh, 2012–2013. Numbers in parentheses indicate rates of *R. felis* positivity for each month; dashed lines indicate monsoon season (June–October).

the 17-kDa antigen gene (186-bp) were identical to that of reference strain *R. felis* URRWXCa12 (GenBank accession no. CP000053). Among all 17-kDa–positive samples, positivity was further confirmed by PCR detection of the *R. felis* 16S rRNA gene and *gltA* in 95% and 75% of samples, respectively. Partial 16S rRNA gene sequences (305-bp) from 12 samples were 100% or 99% (10 and 2 samples, respectively) identical to that of *R. felis* URRWXCa12. The complete open reading frames of *ompA* (1773-bp), partial *ompB* (413-bp), and *gltA* (611-bp) sequences determined for 3, 3, and 5 samples, respectively, were also identical to those of *R. felis* URRWXCa12. The 5 gene sequences were determined for samples from 3 patients (2-year-old girl, 8-year-old boy, 17-year-old boy). The 5 gene sequences from the 2-year-old girl (strain Ric-MMC7) and 2 partial sequences of 16S rRNA (Ric-MMC71 and Ric-MMC133) were deposited in GenBank under accession nos. KP318088–KP318094.

According to PCR, the positivity rate for the *R. felis* 17-kDa antigen gene was higher among male (54%, 40/74) than among female (38%, 29/76) patients and higher among patients in young and old age groups (0–15 years, 57%; 45–60 years, 62%) than among patients in other age groups (15–30 years, 41%; 30–45 years, 44%). During the study period, rates of *R. felis* positivity were highest during the late rainy season of 2012 (September [59%] and October [52%]) and lowest (0%) from December 2012 through April 2013 (Figure). The rate was significantly higher among farmers (76%, 13/17) than among persons of other occupations (e.g., housewives, teachers, students) (42%, 56/133); p = 0.016. Among the 69 rickettsiae-positive patients, headache and myalgia were reported by 29 (42%) and 17 (25%), respectively, whereas rash was detected in only 2 (3%) patients, both of whom were female.

This study demonstrated *R. felis* infection in patients in Bangladesh with unidentified febrile illness. The high prevalence (46%) of *R. felis* infection suggests that this infection is endemic to the north-central area of this country and might be associated with contact between humans of low socioeconomic status and the large number of stray cats and dogs. In contrast, the number of genetically confirmed cases of *R. felis* infection in humans reported to date in China, Taiwan, Thailand, and Laos have been very few (*1*,*2*,*4*,*8*–*10*), although widespread presence of this bacterium in cat fleas has been documented. For further confirmation of spread of this infectious disease, the prevalence of *R. felis* infections among humans, vectors, and reservoirs in other areas in Bangladesh and in other countries in southern Asia should be investigated.

This work was supported in part by a Grant-in-Aid for Scientific Research (grant no. 25305022) from the Japan Society for the Promotion of Science.

References

1. Pérez-Osorio CE, Zavala-Velázquez JE, Arias León JJ, Zavala-Castro JE. *Rickettsia felis* as emergent global threat for humans. Emerg Infect Dis. 2008;14:1019–23. http://dx.doi.org/10.3201/eid1407.071656.
2. Parola P. *Rickettsia felis*: from a rare disease in the USA to a common cause of fever in sub-Saharan Africa. Clin Microbiol Infect. 2011;17:996–1000. http://dx.doi.org/10.1111/j.1469-0691.2011.03516.x.
3. Mediannikov O, Socolovschi C, Edouard S, Fenollar F, Mouffok N, Bassene H, et al. Common epidemiology of *Rickettsia felis* infection and malaria, Africa. Emerg Infect Dis. 2013;19:1775–83. http://dx.doi.org/10.3201/eid1911.130361.
4. Zhang J, Lu G, Kelly P, Zhang Z, Wei L, Yu D, et al. First report of *Rickettsia felis* in China. BMC Infect Dis. 2014;14:682. http://dx.doi.org/10.1186/s12879-014-0682-1
5. Angelakis E, Munasinghe A, Yaddehige I, Liyanapathirana V, Thevanesam V, Bregliano A, et al. Detection of rickettsioses and Q fever in Sri Lanka. Am J Trop Med Hyg. 2012;86:711–2. http://dx.doi.org/10.4269/ajtmh.2012.11-0424.

6. Marié JL, Fournier PE, Rolain JM, Briolant S, Davoust B, Raoult D. Molecular detection of *Bartonella quintana, B. elizabethae, B. koehlerae, B. doshiae, B. taylorii*, and *Rickettsia felis* in rodent fleas collected in Kabul, Afghanistan. Am J Trop Med Hyg. 2006;74:436–9.
7. Schriefer ME, Sacci JB Jr, Dumler JS, Bullen MG, Azad AF. Identification of a novel rickettsial infection in a patient diagnosed with murine typhus. J Clin Microbiol. 1994;32:949–54.
8. Lai CH, Chang LL, Lin JN, Tsai KH, Hung YC, Kuo LL, et al. Human spotted fever group rickettsioses are underappreciated in southern Taiwan, particularly for the species closely-related to *Rickettsia felis.* PLoS ONE. 2014;9:e95810. http://dx.doi.org/10.1371/journal.pone.0095810.
9. Edouard S, Bhengsri S, Dowell SF, Watt G, Parola P, Raoult D. Two human cases of *Rickettsia felis* infection, Thailand. Emerg Infect Dis. 2014;20:1780–1. http://dx.doi.org/10.3201/eid2010.140905.
10. Dittrich S, Phommasone K, Anantatat T, Panyanivong P, Slesak G, Blacksell SD, et al. *Rickettsia felis* infections and comorbid conditions, Laos, 2003–2011. Emerg Infect Dis. 2014;20:1402–4. http://dx.doi.org/10.3201/eid2008.131308.

Address for correspondence: Nobumichi Kobayashi, Department of Hygiene, Sapporo Medical University School of Medicine, S-1 W-17, Chuo-ku, Sapporo 060-8556, Japan; email: nkobayas@sapmed.ac.jp

Malaria Prophylaxis Failure with Doxycycline, Central African Republic, 2014

Marylin Madamet, Tiphaine Gaillard, Guillaume Velut, Cecile Ficko, Pascal Houzé, Claire Bylicki, Stéphane Mérat, Sandrine Houzé, Nicolas Taudon, Rémy Michel, Pierre Pasquier, Christophe Rapp, Bruno Pradines

DOI: http://dx.doi.org/10.3201/eid2108.150524

Author affiliations: Institut de Recherche Biomédicale des Armées, Brétigny sur Orge, France (M. Madamet, N. Taudon, B. Pradines); Aix Marseille Université, Marseille, France (M. Madamet, N. Taudon, B. Pradines); Centre National de Référence du Paludisme, Marseille (M. Madamet, N. Taudon, B. Pradines); Hôpital d'Instruction des Armées Saint Anne, Toulon, France (T. Gaillard); Centre d'Epidémiologie et de Santé Publique des Armées, Marseille, France (G. Velut, R. Michel); Hôpital d'Instruction des Armées Begin, Saint Mandé, France (C. Ficko, S. Mérat, P. Pasquier, C. Rapp); Hôpital Saint-Louis, Paris, France (P. Houzé); Hôpital Bichat Claude Bernard, Paris (S. Houzé); Institut pour la Recherche et le Développement, Paris (S. Houzé), Université Paris Descartes, Paris (S. Houzé); Centre National de Référence du Paludisme, Paris (S. Houzé); Antenne Médicale de Fontevraud, Fontevraud, France (C. Bylicki); Ecole du Val-de-Grâce, Paris (R. Michel, C. Rapp)

To the Editor: Doxycycline is an effective antimalarial prophylactic drug when administered as a monotherapy 1 day before, daily during, and for 4 weeks after travel to an area where malaria is endemic (*1*). Doxycycline is currently a recommended chemoprophylactic regimen for travelers visiting areas where malaria is endemic and has a high prevalence of chloroquine or multidrug resistance (*2*). The World Health Organization also recommends doxycycline in combination with quinine or artesunate as the second-line treatment for uncomplicated *Plasmodium falciparum* malaria (*3*).

Prophylactic and clinical failures of doxycycline against *P. falciparum* have been associated with both inadequate doses (*4*) and poor patient compliance (*5*). However, resistance can also explain failures of prophylaxis. Cycline resistance in *Plasmodium* spp. has been documented as a consequence of selective drug pressure in a *P. berghei* murine malaria model (*6*). The administration of increasing doses of minocycline to mice infected with 1×10^7 parasites for 86 successive passages over 600 days made it possible to obtain a resistant *P. berghei* strain with a median drug inhibitory concentration (IC_{50}) of 600 mg/kg/d, which is 6-fold higher than that of the susceptible starting strain (100 mg/kg/d) (*6*). A Bayesian mixture modeling approach identified 3 different phenotypes (low, medium, and high doxycycline IC_{50} phenotypic groups) among *P. falciparum* clinical isolates (*7,8*). Using 90 isolates from 14 countries, we demonstrated that increases in copy numbers of *P. falciparum* metabolite drug transporter gene (*Pfmdt*, PFE0825w) and *P. falciparum* GTPase TetQ gene (*PfTetQ*, PFL1710c) are associated with reduced susceptibility to doxycycline (*9*); this association was later confirmed (*7*). In addition, isolates with *PfTetQ* KYNNNN motif repeats are associated with in vitro reduced susceptibility to doxycycline and with a significantly higher probability of having an IC_{50} above the doxycycline resistance threshold of 35 mM (*9,10*).

We report a case of documented malaria prophylactic failure with doxycycline in a 26-year-old soldier from France who was infected during a 6-week peacekeeping mission in the Central African Republic in 2014. According to his colleagues and the collective prophylaxis intake, the patient had been compliant with doxycycline prophylaxis. On admission to a hospital in Bangui, Central African Republic, the patient had fever (temperature 40°C), alteration of consciousness, and hypotension. The diagnosis of severe *P. falciparum* malaria was made on the basis of a rapid diagnostic test confirmed by a blood smear test (parasitemia 8% on day 0). Intravenous artesunate was immediately started, in accordance with World Health Organization recommendations (*3*). The patient's clinical condition worsened, and kidney failure developed. Twenty-four hours later (day 1), he was transported by airplane to Bégin Military Teaching Hospital (Saint-Mandé, France). On admission, he had

cerebral edema and a *P. falciparum* parasitemia level of 0.7%. The patient died 1 day later (day 2).

A blood sample obtained from the patient on day 1 in France showed a doxycycline concentration of 195 μg/mL plasma. This concentration, which was determined by liquid chromatography coupled with tandem mass spectrometry, was compatible with a last doxycycline uptake 1 day before diagnosis (day –1). The finding of the expected doxycycline plasma concentration, together with assurances (colleague's statements and collective intake of doxycycline) that the patient had followed the drug regimen, was sufficient to suggest prophylaxis failure in a treatment-compliant patient.

The *P. falciparum* sample obtained from the patient on arrival in France was evaluated for in vitro susceptibility to doxycycline, but the evaluation was unsuccessful. The number of copies of *PfTetQ* and *Pfmdt* genes were evaluated relative to the single-copy *P. falciparum b-tubulin* gene (*pf*β*tubulin*), as previously described (*7,8*). The sample was assayed in triplicate. The $2^{-\Delta\Delta Ct}$ method (where C_t indicates cycle threshold) of relative quantification was used and adapted to estimate the number of copies of *Pfmdt* and *PfTetQ* by using the formula $DDC_t = (C_{t\ (PfTetQ\ \text{or}\ Pfmdt)} - C_{t\ (Pf\beta tubulin)})_{\text{Sample}} - (C_{t\ (PfTetQ\ \text{or}\ Pfmdt)} - C_{t\ (Pf\beta tubulin)})_{\text{Calibrator}}$. Genomic DNA extracted from 3D7 *P. falciparum*, which has a single copy of each gene, was used for calibrator sample; *Pf*β*tubulin* served as the control housekeeping gene. The experiment was assayed twice. The sample had 2 copies of *PfTetQ* and *Pfmdt* genes, which suggested decreased in vitro susceptibility of the sample to doxycycline (*8,9*). The genotyping of *PfTetQ* sequence polymorphisms was done by using conventional methods with the primers *PfTetQ* forward (5'-TCACGACAAATGTGCTAGATAC-3') and *PfTetQ* reverse (5'-ATCATCATTTGTGGTGGATAT-3'), as previously described (*10*). Two *PfTetQ* KYNNNN motif repeats were found in the sample; <3 KYNNNN motif repeats are predictive of in vitro *P. falciparum*–resistant parasites with an IC_{50} of >35 mM (odds ratio 15) (*10*). The 2 copies of *Pfmdt* and the 2 KYNNNN motif repeats have been shown to be associated with parasites with in vitro resistance to doxycycline (*9,10*). The association of doxycycline resistance (prophylactic failure with statement of correct intake and the presence of an expected concentration) with increased *Pfmdt* copies and decreased *PfTetQ* KYNNNN motif repeats suggest that these molecular markers are predictive markers of doxycycline resistance that can be used for resistance surveillance.

References

1. Briolant S, Fusaï T, Rogier C, Pradines B. Tetracycline antibiotics in malaria. Open Trop Med J. 2008;1:31–46. http://dx.doi.org/10.2174/1874315300801010031
2. Institut National de Veille Sanitaire. Recommandations sanitaires pour les voyageurs, 2014. Bulletin Epidémiologique Hebdomadaire. 2014;16–17:264–311.
3. World Health Organization. Guidelines for the treatment of malaria, 2nd ed. Geneva: The Organization; 2010.
4. Pang L, Limsomwong N, Singharaj P. Prophylactic treatment of vivax and falciparum malaria with low-dose doxycycline. J Infect Dis. 1988;158:1124–7. http://dx.doi.org/10.1093/infdis/158.5.1124
5. Wallace MR, Sharp TW, Smoak B, Iriye C, Rozmajzl P, Thornton SA, et al. Malaria among United States troops in Somalia. Am J Med. 1996;100:49–55. http://dx.doi.org/10.1016/S0002-9343(96)90011-X
6. Jacobs RL, Koontz LC. *Plasmodium berghei*: development of resistance to clindamycin and minocycline in mice. Exp Parasitol. 1976;40:116–23. http://dx.doi.org/10.1016/0014-4894(76)90073-4
7. Briolant S, Baragatti M, Parola P, Simon F, Tall A, Sokhna C, et al. Multinormal in vitro distribution model suitable for the distribution of *Plasmodium falciparum* chemosusceptibility to doxycycline. Antimicrob Agents Chemother. 2009;53:688–95. http://dx.doi.org/10.1128/AAC.00546-08
8. Gaillard T, Briolant S, Houzé S, Baragatti M, Wurtz N, Hubert V, et al. *PftetQ* and *pfmdt* copy numbers as predictive molecular markers of decreased ex vivo doxycycline susceptibility in imported *Plasmodium falciparum* malaria. Malar J. 2013;12:414. http://dx.doi.org/10.1186/1475-2875-12-414
9. Briolant S, Wurtz N, Zettor A, Rogier C, Pradines B. Susceptibility of *Plasmodium falciparum* isolates to doxycycline is associated with *pftetQ* sequence polymorphisms and *pftetQ* and *pfmdt* copy numbers. J Infect Dis. 2010;201:153–9. http://dx.doi.org/10.1086/648594
10. Achieng AO, Ingasia LA, Juma DW, Cheruiyot AC, Okudo CA, Yeda RA, et al. Reduced in vitro doxycycline susceptibility in Plasmodium falciparum field isolates from Kenya is associated with PftetQ KYNNNN sequence polymorphism. Antimicrob Agents Chemother. 2014;58:5894–9. http://dx.doi.org/10.1128/AAC.02788-13

Address for correspondence: Bruno Pradines, Unité de parasitologie et d'entomologie, Institut de recherche biomédicale des Armées, BP 73, 91223 Brétigny sur Orge, France; email: bruno.pradines@free.fr

Avian Gyrovirus 2 DNA in Fowl from Live Poultry Markets and in Healthy Humans, China

Jianqiang Ye,[1] Xiaoyan Tian,[1] Quan Xie, Yu Zhang, Yuanzhao Sheng, Zhenwen Zhang, Chengming Wang, Hong Zhu, Yumeng Wang, Hongxia Shao, Aijian Qin

Author affiliations: Ministry of Education Key Laboratory for Avian Preventive Medicine and Key Laboratory of Jiangsu Preventive Veterinary Medicine, Yangzhou University, Yangzhou, China (J. Ye, X. Tian, Q. Xie, Y. Zhang, Y. Sheng, H. Zhu, Y. Wang, H. Shao, A. Qin); Jiangsu Co-innovation Center for Prevention and Control of Important Animal Infectious Diseases and Zoonoses, Yangzhou (J. Ye, Z. Zhang, C. Wang, H. Shao, A. Qin); College of Medicine, Yangzhou University, Yangzhou (Z. Zhang)

DOI: http://dx.doi.org/10.3201/eid2108.150203

[1]These authors contributed equally to this article.

To the Editor: In 2011, a chicken anemia virus (CAV)–related sequence, designated avian gyrovirus 2 (AGV2), was first identified in serum samples from diseased chickens in Brazil (*1*). During the same year, a human gyrovirus (HGyV) sequence that had high identity to AGV2 was detected in the skin of humans in France (*2*). As with CAV, 3 open reading frames (ORFs) for encoding viral proteins (VP) 1–3 (*2*) overlapped in genome of AGV2. Recently, HGyV/AGV2 has been detected in Hong Kong in chicken meat for consumption by humans, in human blood samples from donors in France, and in HIV-positive persons and organ transplant recipients in Italy and the United States (*3*–*5*). However, the epidemiology, host range, transmission route, and pathogenesis of AGV2 remain poorly understood. Bullenkamp et al. found that AGV2 VP3 protein, like CAV VP3, can induce apoptosis of tumor cells (*6*). Also, Abolnik et al. reported the detection in Southern Africa of AGV2 in brain tissue of chickens that showed severe neurologic signs (*7*). These findings highlight the potential pathogenesis of AGV2.

So far, little is known about AGV2 in mainland China among chickens and humans. Because live poultry market (LPMs) play a critical role in the transmission of poultry pathogens to humans, we used PCR to investigate the presence of AGV2 in chickens (54 feather shaft samples) from 4 LPMs in Yangzhou and in 178 human blood samples from healthy persons living in Yangzhou. The DNA from the feather shafts and human blood were extracted as previously described (*8*). PCR was performed by using the following 2 primers: AGV2_F 5′−CGTGTCCGCCAGCAGAAACGAC-′3 and AGV2_R 5′-GGTAGAAGCCAAAGCGTCCACGA-′3. The PCR targets partial VP2 and VP3 genes that have an expected size of 346 bp. The parameters of the PCR were as follows: 1 cycle at 95°C for 5 min; then 30 cycles at 94°C for 30 s, 64°C for 30 s, and 72°C for 30 s; and 1 cycle at 72°C for 10 min. PCR showed that a band with the size of ≈346 bp could be amplified in 10 of 54 chicken feather samples and in 2 of 178 human blood samples.

We confirmed the AGV2 specificity of these PCR–amplified bands by direct sequencing using the Sanger method. The sequence assay showed that the 12 sequences identified here had 98.3%–100% homology to each other and 92.2%–99.1% aa identity to AGV2 samples previously deposited in GenBank (see Figure legend for accession numbers). The positive rates for samples from the 4 LPMs tested were 25%, 12.5%, 15.8%, and 20%; the positive rate for the 178 human blood samples was 1.1%. The low positive frequency of AGV2 in human blood detected in this study is consistent with that found by investigation in other countries (*3,4*). Because the limit of detection of PCR in this study was estimated to be 2.7 copies of AGV2 DNA using dilutions of a plasmid with partial AGV2 sequence, we determined that the copy number of AGV2 in the 2 positive human blood samples was 2.7×10^3 copies/mL plasma.

We also constructed a phylogenetic tree using the neighbor-joining method (1,000 bootstrap replications) with MEGA6 (*9*). The tree analysis revealed that the 12 AGV2 isolates we identified and 7 AGV2 isolates from GenBank clustered into 2 subgroups on the basis of the PCR amplified fragment (Figure). The 12 AGV2 sequences we identified clustered together with gyrovirus sequences detected in ferret and human samples in subgroup I, and the prototype sequence Ave3 was located in subgroup II. The 12 AGV2 showed ≈92.2%–93% aa identity to Ave3, and <99.1% homology with isolates CL33, G13, and 915F06007 detected in ferret and human samples. The 12

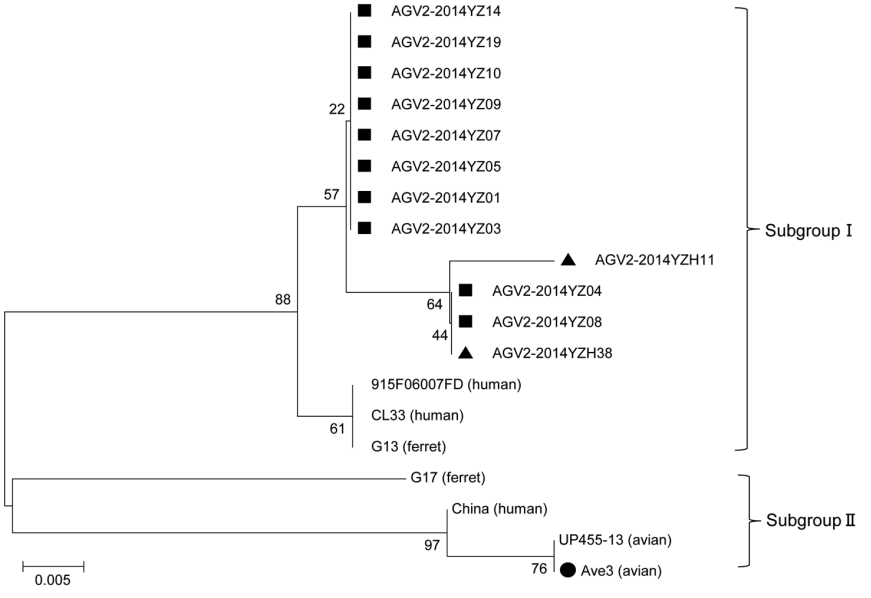

Figure. Phylogenetic analysis of AGV2. The phylogenetic tree was constructed by using the neighbor-joining method (1,000 bootstraps) with MEGA6 (9). Black squares indicate the 10 AGV2 identified from live poultry markets; black triangles indicate the 2 AGV2 identifed from human blood; black dot indicates the prototype AGV2 sequence. Sequences and GenBank accession nos.: AGV2–2014YZ01, KP993124; AGV2–2014YZ03, KP993125; AGV2–2014YZ04, KP993126; AGV2–2014YZ05, KP993127; AGV2–2014YZ07, KP993128; AGV2–2014YZ08, KP993129; AGV2–2014YZ09, KP993130; AGV2–2014YZ10, KP993131; AGV2–2014YZ14, KP993132; AGV2–2014YZ19, KP993133; AGV2–2014YZH11, KP993134; AGV2–2014YZH38, KP993135; 915 F 06 007 FD, FR823283; CL33, JQ308212; G13, KJ452214; G17, KJ452213; China, JQ690763; UP455–13, KF436510; Ave3, HM590588. Scale bar indicates amino acid substitutions per site.

AGV2 sequences also showed ≈93%–93.9% identities to ACV2 sequence that was previously identified in human fecal samples from mainland China (GenBank accession no. JQ690763). The China sequence also clustered with Ave3 in subgroup II. These findings indicate that ≥2 subgroups of AGV2 are circulating in mainland China.

Our results demonstrate the presence of AGV2 in LPMs and human blood in mainland China. The amplification and analysis of partial AGV2 sequences was the major limitation in our method. The high homology between sequences identified in LPMs and human blood indicates the LPMs are a potential source for AGV2 in humans. Unlike our 12 conserved AGV2, AGV2 identified by Santos et al. in southern Brazil varied <15.8%, and these variants of AGV2 were mainly detected in diseased chickens (*8*). However, little is known about the molecular epidemiology of these AGV2 variants in other countries. More recently, Varela et al. reported the detection of AGV2 in poultry vaccines, indicating the potential role of contaminated vaccines in the spread of AGV2 (*10*). Future studies should investigate the large geographic distribution of AGV2 and monitor the variants, the host range, and the associated diseases.

This work was supported by the National Natural Science Foundation of China (31402228), National College Student Innovation Training Project (201411117002), Key University Science Research Project of Jiangsu Province (14KJA230002), Jiangsu Province College Student Innovation training Projects (201411117002Z and 201411117056Y), and the Priority Academic Program Development of Jiangsu Higher Education Institutions.

References

1. Rijsewijk FA, Dos Santos HF, Teixeira TF, Cibulski SP, Varela AP, Dezen D, et al. Discovery of a genome of a distant relative of chicken anemia virus reveals a new member of the genus Gyrovirus. Arch Virol. 2011;156:1097–100. http://dx.doi.org/ 10.1007/s00705-011-0971-6
2. Sauvage V, Cheval J, Foulongne V, Gouilh MA, Pariente K, Manuguerra JC, et al. Identification of the first human gyrovirus, a virus related to chicken anemia virus. J Virol. 2011;85:7948–50. http://dx.doi.org/10.1128/JVI.00639-11
3. Maggi F, Macera L, Focosi D, Vatteroni ML, Boggi U, Antonelli G, et al. Human gyrovirus DNA in human blood, Italy. Emerg Infect Dis. 2012;18:956–9. http://dx.doi.org/10.3201/eid1806.120179
4. Biagini P, Bedarida S, Touinssi M, Galicher V, de Micco P. Human gyrovirus in healthy blood donors, France. Emerg Infect Dis. 2013;19:1014–5. http://dx.doi.org/10.3201/eid1906.130228
5. Chu DK, Poon LL, Chiu SS, Chan KH, Ng EM, Bauer I, et al. Characterization of a novel gyrovirus in human stool and chicken meat. J Clin Virol. 2012;55:209–13. http://dx.doi.org/10.1016/j.jcv.2012.07.001
6. J Bullenkamp DC, Malik F, Alkhatabi H, Kulasekararaj A, Odell EW, Farzaneh F, Gäken J, et al. Human gyrovirus apoptin shows a similar subcellular distribution pattern and apoptosis induction as the chicken anaemia virus derived VP3/Apoptin. Cell Death Dis. 2012;3:e296. http://dx.doi.org/10.1038/cddis.2012.34
7. Abolnik C, Wandrag DB. Avian gyrovirus 2 and a virulent Newcastle disease virus coinfection in a chicken flock with neurologic symptoms and high mortalities. Avian Dis. 2014; 58:90–4. http://dx.doi.org/10.1637/10657-090313-Reg.1
8. dos Santos HF, Knak MB, de Castro FL, Slongo J, Ritterbusch GA, Klein TA, et al. Variants of the recently discovered avian gyrovirus 2 are detected in southern Brazil and the Netherlands. Vet Microbiol. 2012;155:230–6. http://dx.doi.org/10.1016/j.vetmic.2011.09.021
9. Tamura K, Stecher G, Peterson D, Filipski A, Kumar S. MEGA6: Molecular Evolutionary Genetics Analysis version 6.0. Mol Biol Evol. 2013;30:2725–9. http://dx.doi.org/10.1093/molbev/mst197
10. Varela AP, Dos Santos HF, Cibulski SP, Scheffer CM, Schmidt C, Sales Lima FE, et al. Chicken anemia virus and avian gyrovirus 2 as contaminants in poultry vaccines. Biologicals. 2014;42:346–50. http://dx.doi.org/10.1016/j.biologicals.2014.08.002

Address for correspondence: Jianqiang Ye, Yangzhou University, 12 Wenhui East Rd, Yangzhou, Jiangsu, 225009, China; email: jqye@yzu.edu.cn, hxshao@yz.edu.cn; aijian@yzu.edu.cn

Mapping Disease Transmission Risk: Enriching Models Using Biogeography and Ecology

A. Townsend Peterson

Johns Hopkins University Press, Baltimore, Maryland, USA, 2014

ISBN 13: 978-1-4214-1473-7

ISBN 10: 1-4214-1473-2

Pages: 210; Price: US $79.95 (hardcover)

Global human population density is increasing, as are our abilities to assemble large ecologic datasets and perform surveillance for and respond to diseases as they emerge. Consequently, multidimensional ecologic data may help us improve public health locally and globally. This engaging book empowers disease modelers and public health policy makers by introducing them to ecologic niche models as predictors of disease transmission risk.

Part I describes distributional ecology, contrasting the ecologic approach that takes into account multiple layers of distributional data with an approach that only plots disease cases or absences. Part II elaborates on the kinds of data necessary to develop ecologic models rather than arbitrarily complex "black box" models. Part III critiques poor study design and data assembly and demonstrates how not to construct a dataset. Part IV summarizes approaches to calibrating, processing, and evaluating models and the production of risk maps, warning readers about the complex factors that are associated with human society.

Peterson presents examples where models calibrated for one dataset are used to transfer rules to another dataset to assess risk. By contrasting these models with models that incorporate only disease cases, Peterson shows how to define the niche of vectors of disease where occurrence data are rich, then evaluate the potential presence of the niche in novel locales or across changing environments, yielding the risk of emergence.

In this book, Peterson has put together an easy read that demonstrates his expertise and persuasively frames disease transmission risk in terms of niche models. A reader already convinced that understanding the geography of ecologic interactions is essential to public health disease modeling may want to pick up a more technical book that addresses ecologic niche modeling in detail. For readers interested in mechanistic models, Mapping Disease Transmission Risk is not the right book. Peterson could have handled some of the issues about the relative value and weighting of presence and absence data by using appropriate likelihood models of the observation process itself. Bayesian analyses could obviate many of the issues of uncertainty associated with low counts and zero-observation cells. However, for readers who would like to move into the geographic mapping of disease emergence and aren't sure where to start, this book provides many dos and don'ts and references that could jump-start a project.

Peterson concludes by noting the historical link between public health and geographic mapping. As we begin to view and quantify every foot of the Earth we depend on, it becomes increasingly possible and necessary to incorporate many layers of knowledge to guide policy for human—and ecological—health. To quote Martin Luther King, Jr., "It really boils down to this: that all life is interrelated. We are all caught in an inescapable network of mutuality, tied together into a single garment of destiny. Whatever affects one directly, affects all indirectly" (*1*).

Jeffrey Townsend

Author affiliation: Yale School of Public Health, New Haven, Connecticut, USA

References

1. King ML Jr. A Christmas sermon on peace (1967). In: Washington JM, editor. A testament of hope: the essential writings and speeches of Martin Luther King, Jr. New York: HarperCollins; 1986. p. 253–8.

Address for correspondence: Jeffrey Townsend, Yale University, 135 College St., New Haven, CT 06525, USA; email: jeffrey.townsend@yale.edu

Correction: Vol. 21, No. 4

An incorrect version of the Technical Appendix was provided online for the article Population Structure and Antimicrobial Resistance of Invasive Serotype IV Group B Streptococcus, Toronto, Ontario, Canada (S. Teatero et al.). The article has been corrected online (http://wwwnc.cdc.gov/eid/article/21/4/14-0759_article).

Cornelius Norbertus Gijsbrechts (ca 1630−after 1683) *Trompe l'oeil with Studio Wall and Vanitas Still Life*, 1668. Oil on canvas. 59.84 x 46.46 in / 152 x 118 cm. Digital image from the public domain collection, Statens Museum for Kunst, Copenhagen.

Beyond First Impressions

Byron Breedlove and Jared Friedberg

Few details endure about the life and family circumstances of Flemish painter Cornelius Norbertus Gijsbrechts. We know that he was born in Antwerp, Belgium, and his talent earned him a position of court painter with two Danish kings, Frederick III (1609–1675) and Christian V (1646–1699). In 1660, Gijsbrechts was accorded membership in the prominent, influential Guild of St. Luke. Over his career, the artist worked in various locations, including Antwerp, Regensburg, Hamburg, and Copenhagen, and it was in the latter city where he created his signature series of trompe l'oeil (deception of the eye) paintings during 1668–1672.

Trompe l'oeil, a subgenre of still life painting, embraces use of realistic imagery to create an optical illusion of depth in works that can be perceived as real, three-dimensional objects rather than flat paintings. It flourished from the Renaissance onward, though murals of trompe l'oeil art are found among the ruins of Pompeii and Herculaneum and remain popular today. According to the National Gallery of Art, "The discovery of perspective in fifteenth-century Italy and advancements in the science of optics in the seventeenth-century Netherlands enabled artists to render objects and spaces with eye-fooling exactitude."

This month's cover painting *Trompe l'oeil with Studio Wall and Vanitas Still Life* is a prime example of this inventive subterfuge and also of a vanitas painting, a meditation on mortality. Gijsbrechts makes a skull the focal point of the painting, ensuring no one misses his allusion to the temporal nature of life. Other symbols supports the theme of transience: smoke trailing from an extinguished candle and an hourglass tipped on its side symbolize death; a violin, tankard, clay pipe, and tobacco represent fleeting pleasures. The unity of these symbols represent the ebb and flow of birth, death, and resurrection, encouraging both a wistful examination of life's purpose and a solemn acceptance of death's finality.

Author affiliations: Centers for Disease Control and Prevention, Atlanta, Georgia, USA (B. Breedlove); Northrop Grumman, Atlanta, Georgia, USA (J. Friedberg)

DOI: http://dx.doi.org/10.3201/eid2108.AC2108

Gijsbrechts pulls the scene back and reveals the vanitas on a temporary canvas hung on a wooden wall, surrounded by the tools of his craft, including brushes and a palette featuring the colors he used in his construction of the painting. A miniature self-portrait affixed to the frame reminds viewers that art endures beyond the life of the artist. Those who fall for the deception and perceive the vanitas as the sole painting miss the message that Gijsbrechts intends: nothing is what it seems without context.

In trompe l'oeil, the background imagery surrounding the painting's center provides perspective and clues that engage viewers and contribute to understanding the overall work. Disease surveillance for emerging infections relies on a somewhat similar, albeit more complicated process. To gain perspective, one must assess a complex but incomplete set of intertwined, dynamic factors, which may include antimicrobial drug resistance, climate change, food production practices, global mobility, the route(s) of transmission of the etiologic agents, and ecology of the pathogens.

By their nature, surveillance data are representative of disease in populations, and they are always incomplete and sometimes inaccurate. It takes a critical, well-prepared mind to properly interpret and analyze the meaning and significance of surveillance data or unravel clues about how an emerging infectious disease spreads. Gijsbrechts' portrait displays the tools and medium that he used to construct his illusion, but not everyone who views the painting will come to this realization. The experience of viewing a trompe l'oeil reminds us that seeing beyond our initial assumptions—whether we are studying art, investigating the outbreak of an emerging infection, or analyzing reams of data—requires that we connect background information, delve beyond the surface, and recognize patterns and aberrations.

Bibliography

1. Institute of Medicine. Global infectious disease surveillance and detection: assessing the challenges—finding solutions. Workshop summary. Washington (DC): The National Academies Press; 2007.
2. National Gallery of Denmark. Statens Museum for Kunst. Cornelius Norbertus Gijsbrechts (c. 1610–after 1675), trompe l'oeil with studio wall and vanitas still life, 1668 [cited 2015 Jun 3]. http://www.smk.dk/en/explore-the-art/highlights/cornelius-norbertus-gijsbrechts-trompe-loeil-with-studio-wall-and-vanitas-still-life/
3. National Gallery of Denmark. Statens Museum for Kunst. Cornelius Norbertus Gijsbrechts (c. 1610–after 1675), Trompe l'oeil. A cabinet in the artist's studio, 1670–1671 [cited 2015 Jun 3]. http://www.smk.dk/en/explore-the-art/highlights/cornelius-norbertus-gijsbrechts-trompe-loeil-a-cabinet-in-the-artists-studio/
4. National Gallery of Art. Deceptions and illusions: five centuries of trompe l'oeil painting [cited 2015 Jun 8]. http://www.nga.gov/exhibitions/trompe-info.htm
5. Nuzzo JB. Global surveillance for emerging infectious diseases. M'ikanatha NM, Isklander J, editors. In: Concepts and methods in infectious disease surveillance. New York: Wiley Blackwell; 2015. p. 177–85.

Address for correspondence: Byron Breedlove, EID Journal, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mailstop C17, Atlanta, GA 30329-4027, USA; email: wbb1@cdc.gov

EMERGING INFECTIOUS DISEASES®

Upcoming Issue

- Use of Pneumococcal Disease Epidemiology to Set Policy and Prevent Disease during 20 Years of the Emerging Infections Program
- Twenty Years of Active Bacterial Core Surveillance
- The US Influenza Hospitalization Surveillance Network
- Monitoring Effect of Human Papillomavirus Vaccines in US Population, Emerging Infections Program, 2008–2012
- Emerging Infections Program—State Health Department Perspective
- Effect of Culture-Independent Diagnostic Tests on Future Emerging Infections Program Surveillance
- Tracking Pertussis and Evaluating Control Measures by Enhanced Pertussis Surveillance System, Emerging Infections Program Network, United States
- Improving Accuracy of Influenza-Associated Hospitalization Rate Estimates
- Estimations of Lyme Disease Cases, United States, 2005–2010
- Emerging Infections Program and Antimicrobial Drug Resistance Surveillance
- Cultivating an Adaptive Domestic Network for Surveillance and Evaluation of Emerging Infections
- Third Wave of Influenza A(H7N9) Virus from Poultry, Guangdong Province, China, 2014–2015
- Putative Lineage of Novel African Usutu Virus, Central Europe
- Laboratory Testing for Middle East Respiratory Syndrome Coronavirus, California, USA, 2013–2014
- Follow-up of Contacts of Middle East Respiratory Syndrome Coronavirus–Infected Returning Travelers, the Netherlands, 2014
- Acute Respiratory Infections in Travelers Returning from MERS-CoV–Affected Areas

Complete list of articles in the September issue at
http://www.cdc.gov/eid/upcoming.htm

Upcoming Infectious Disease Activities

August 24–26, 2015
ICEID
International Conference on Emerging Infectious Diseases
Atlanta, GA, USA
http://www.iceid.org/

August 29–September 2, 2015
IDBR
20th Annual Infectious Disease Board Review Course
McLean, VA, USA
http://smhs.gwu.edu/cehp/activities/courses/idbr

September 17–21, 2015
ICAAC
Interscience Conference on Antimicrobial Agents and Chemotherapy
San Diego, CA, USA

October 25–29, 2015
ASTMH
American Society of Tropical Medicine and Hygiene
64th Annual Meeting
Philadelphia, Pennsylvania
info@astmh.org

December 6–9, 2015
2015 National HIV Prevention Conference
Atlanta, GA
http://www.cdc.gov/nhpc/index.html

February 8–10, 2016
ASM Biodefense and Emerging Diseases Research Meeting
Arlington, VA, USA
biodefense@asmusa.org

March 2–5, 2016
ISID
17th International Congress on Infectious Diseases
Hyderabad, India
activities/courses/idbr

To submit an announcement, send an email message to EIDEditor (eideditor@cdc.gov). Include the date of the event, the location, the sponsoring organization(s), and a website that readers may visit or a telephone number or email address that readers may contact for more information.

Announcements may be posted on the journal Web page only, depending on the event date.

Earning CME Credit

To obtain credit, you should first read the journal article. After reading the article, you should be able to answer the following, related, multiple-choice questions. To complete the questions (with a minimum 75% passing score) and earn continuing medical education (CME) credit, please go to http://www.medscape.org/journal/eid. Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers. You must be a registered user on Medscape.org. If you are not registered on Medscape.org, please click on the "Register" link on the right hand side of the website to register. Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. For questions regarding the content of this activity, contact the accredited provider, CME@medscape.net. For technical assistance, contact CME@webmd.net. American Medical Association's Physician's Recognition Award (AMA PRA) credits are accepted in the US as evidence of participation in CME activities. For further information on this award, please refer to http://www.ama-assn.org/ama/pub/about-ama/awards/ama-physicians-recognition-award.page. The AMA has determined that physicians not licensed in the US who participate in this CME activity are eligible for AMA PRA Category 1 Credits™. Through agreements that the AMA has made with agencies in some countries, AMA PRA credit may be acceptable as evidence of participation in CME activities. If you are not licensed in the US, please complete the questions online, print the certificate and present it to your national medical association for review.

Article Title:

Escherichia coli O157 Outbreaks in the United States, 2003–2012

CME Questions

1. You recently treated a 28-year-old man with a 3-day history of bloody diarrhea. His stool culture returns with positive results for *Escherichia coli* O157. In the current study by Heiman and colleagues, what was the most common source of outbreaks of *E. coli* O157?

A. Foodborne
B. Person-to-person
C. Animal contact
D. Other/unknown

2. Which of the following specific foods was associated with the majority of foodborne cases of *E. coli* O157 in the current study?

A. Beef
B. Dairy
C. Leafy vegetables
D. Poultry

3. You call the patient with the laboratory result, and he is feeling somewhat better since starting antibiotics. Which of the following statements regarding the severity of illness with *E. coli* O157 in the current study is most accurate?

A. Person-to-person outbreaks accounted for the majority of cases of mortality
B. Person-to-person outbreaks were associated with the highest rates of hospitalization
C. Hemolytic uremic syndrome was most associated with outbreaks from animal contact
D. Outbreaks related to beef were associated with the highest rates of hospitalization

4. What else should you consider regarding the epidemiology of *E. coli* O157 outbreaks in the current study?

A. Nearly 80% of patients were men
B. Most cases occurred in the winter
C. Outbreaks were more common in Southern vs Northern states
D. More than 80% of waterborne outbreaks were reported in states that border the Mississippi River

Activity Evaluation

1. The activity supported the learning objectives.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
2. The material was organized clearly for learning to occur.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
3. The content learned from this activity will impact my practice.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
4. The activity was presented objectively and free of commercial bias.				
Strongly Disagree				Strongly Agree
1	2	3	4	5

Earning CME Credit

To obtain credit, you should first read the journal article. After reading the article, you should be able to answer the following, related, multiple-choice questions. To complete the questions (with a minimum 75% passing score) and earn continuing medical education (CME) credit, please go to http://www.medscape.org/journal/eid. Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers. You must be a registered user on Medscape.org. If you are not registered on Medscape.org, please click on the "Register" link on the right hand side of the website to register. Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. For questions regarding the content of this activity, contact the accredited provider, CME@medscape.net. For technical assistance, contact CME@webmd.net. American Medical Association's Physician's Recognition Award (AMA PRA) credits are accepted in the US as evidence of participation in CME activities. For further information on this award, please refer to http://www.ama-assn.org/ama/pub/about-ama/awards/ama-physicians-recognition-award.page. The AMA has determined that physicians not licensed in the US who participate in this CME activity are eligible for AMA PRA Category 1 Credits™. Through agreements that the AMA has made with agencies in some countries, AMA PRA credit may be acceptable as evidence of participation in CME activities. If you are not licensed in the US, please complete the questions online, print the certificate and present it to your national medical association for review.

Article Title

Community-Based Outbreak of *Neisseria meningitidis* Serogroup C Infection in Men who Have Sex with Men, New York City, New York, USA, 2010–2013

CME Questions

1. Which of the following statements regarding invasive meningococcal disease in general and its prevention is most accurate?

A. Approximately half of cases are fatal
B. The rate of serious long-term complications exceeds 10%
C. Young adults carry the highest risk
D. No booster for the meningococcal vaccine is required if it is delivered by age 11 years

2. Which of the following statements regarding the epidemiology and outcomes of the serogroup C invasive meningococcal disease (MenC) outbreak described in the current study is most accurate?

A. Approximately half of individuals affected in the outbreak were men who have sex with men (MSM)
B. Most cases were fatal
C. Nearly all patients were white
D. More than half of participants with data available had used electronic tools to find sexual partners

3. Which of the following statements regarding the vaccine campaign against meningitis in the current study is most accurate?

A. Less than 1,500 vaccine doses were distributed during the outbreak
B. Free vaccine events at bars and clubs were highly successful
C. Vaccine events hosted by clinicians occurred solely in medical offices
D. Vaccine events hosted by clinicians were successful overall

4. Which of the following elements of the meningococcal vaccination outreach campaign described in the current study was most effective?

A. Email
B. Banner advertisements on websites
C. Articles in The New York Times
D. Pop-up advertisements on mobile applications

Activity Evaluation

1. The activity supported the learning objectives.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
2. The material was organized clearly for learning to occur.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
3. The content learned from this activity will impact my practice.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
4. The activity was presented objectively and free of commercial bias.				
Strongly Disagree				Strongly Agree
1	2	3	4	5

Visit www.cdc.gov/vaccines/parents. Learn about the vaccines your baby needs from a reliable source. The CDC's website explains the 14 diseases vaccines prevent, CDC's recommended schedule, possible side effects, how to comfort your baby during vaccine visits and more. Talk to your child's doctor, and visit our website to get the facts about vaccines.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Immunization. Power to Protect.